



## Diabetes

Beginning with the discovery of insulin by Dr. Frederick Banting and Charles Best in 1921, research has provided the foundation for every advance in the understanding, treatment, and prevention of diabetes. The insights gleaned from explorations in many scientific disciplines have steadily contributed to a growing knowledge base that guides and inspires the scientists of today. Many of these gains, which have led to concrete improvements in survival and quality of life for people with diabetes, can be traced to research and research training supported by the NIH.

With the knowledge gained from NIH-supported research, doctors now use simple blood tests to diagnose diabetes and to assess long-term blood glucose control. They better understand the importance of blood glucose control in preventing complications. They can prescribe new classes of oral drugs and combinations of drugs that delay the need for insulin treatment in people with type 2 diabetes. They can also better manage the risk factors for heart disease, a major killer of people with diabetes, and to delay or prevent blindness from diabetes. People who suffer from kidney failure, another diabetes complication, are leading longer lives due to improvements in dialysis and kidney transplantation. Now more than ever before, the burden of diabetes in all its forms is giving way to understanding and hope as researchers unravel its complex mysteries and move steadily closer to improved treatments and, ultimately, cures.

Sixteen million people in the United States have diabetes mellitus, a chronic disease that lowers average life expectancy by up to 15 years and often leads to painful, debilitating complications. Diabetes is the main cause of kidney failure, adult blindness, and non-traumatic amputations in America and a

major risk factor for heart disease, stroke, and birth defects.

There are several different forms of diabetes. Up to 10 percent of people with diabetes have type 1, formerly known as juvenile onset or insulin-dependent diabetes. Type 1 diabetes develops when the body's immune

### Diabetes in 1950

- The disease has been recognized for more than 2,000 years.
- Banting and Best discovered insulin 25 years earlier.
- Treatment is beef-pork insulin injections.
- Patients measure glucose in urine to monitor treatment.

#### *In 1950, a person with diabetes must wait:*

- 2 years for Lente insulin
- 6 years for oral drugs for type 2 diabetes
- 11 years for glucose strips
- 22 years for the glucometer
- 26 years for the Hemoglobin A1C test
- 31 years for human insulin
- 43 years for the Diabetes Control and Complications Trial findings
- 50 years for the first promising trial in islet transplantation

#### *And in 1950, researchers must wait:*

- 3 years for Watson and Crick to describe the structure of DNA
- 6 years for a determination of insulin's amino acid sequence
- 10 years for a radioimmunoassay for insulin
- 15 years for the concept of phosphorylation in hormone action
- 17 years for a description of insulin's crystal structure
- 20 years for a direct demonstration of insulin receptors
- 30 years for the cloning of human insulin cDNA
- 50 years for identification of the NIDDM1 gene

*Adapted from slides of Dr. C. Ronald Kahn, Joslin Diabetes Center*

system destroys pancreatic beta cells, the only cells in the body that sense blood sugar and secrete the hormone insulin, which regulates blood sugar. This form of diabetes usually strikes children and young adults, who require daily or more frequent insulin injections or use of an insulin pump for the rest of their lives. Insulin treatment, however, is not a cure, nor can it reliably prevent the long-term complications of the disease.

Type 2 diabetes, which accounts for about 90 percent of diabetes cases in the United States, is most common in adults over age 40. Affecting about 6 percent of the U.S. population, it is strongly associated with obesity (more than 80 percent of people with type 2 diabetes are overweight), inactivity, family history of diabetes, and racial or ethnic background. With the aging of Americans

and the alarming increase in obesity in all ages and ethnic groups, the incidence of type 2 diabetes has also been rising nationwide.

People with this form of diabetes first develop insulin resistance, a disorder in which muscle, fat, and liver cells do not use insulin properly. At first, the pancreas compensates by producing more insulin, but gradually its capacity to secrete insulin in response to meals falters, and the timing of insulin secretion is abnormal. After diabetes develops, pancreatic production of insulin continues to decline. Many people can control their blood glucose by following a careful diet and exercise program, losing excess weight, and taking oral medication. However, the longer a person has type 2 diabetes, the more likely he or she will need insulin injections, either alone or combined with oral drugs.

Once seen only as an adult disease, type 2 diabetes has been increasing in children and adolescents. National data on this form of diabetes in children are lacking, but some clinics have reported that as many as one-third of children with new-onset diabetes have type 2, and more than three-quarters of these children are minorities. High-fat, high-calorie diets and lack of exercise are probably the main reasons for the rising incidence of children with this disease. The NIDDK is urgently funding more research to prevent and treat type 2 diabetes in children, especially in minority communities.

Gestational diabetes, which occurs in about 3 to 5 percent of pregnancies, generally resolves after childbirth, though the mother has a higher risk of getting type 2 diabetes years later. Also, her child is more prone to developing obesity and type 2 diabetes in adulthood.



NIDDK Diabetes Clinic in Arizona

## Diabetes in Minorities

For reasons poorly understood, African Americans, Hispanic/Latino Americans, American Indians, and some Asian Americans and Pacific Islanders are at especially high risk for type 2 diabetes. In the United States, about 25 per cent of all adults with diabetes and most children and adolescents with type 2 diabetes are minorities. Minorities are also more likely to develop the microvascular complications of diabetes and to have more lower limb amputations than non-minorities with diabetes.

Since 1965, the NIDDK has conducted a research program in Arizona's Pima Indians, a population with a high incidence of obesity and type 2 diabetes. In recent years, the program has been expanded to include genetic studies, intervention trials, and studies to prevent and treat diabetes and its complications in this population (see page 39). NIDDK researchers have found that children born to a mother with diabetes during pregnancy have a greatly increased risk of becoming obese and developing type 2 diabetes at an early age. A girl whose mother had diabetes during pregnancy is more likely to have

### Diabetes in America

- Afflicts 16 million people
- 800,000 new cases a year
- One-third of cases are undiagnosed
- Sixth leading cause of death from disease
- Highest incidence in minorities
- Main cause of new blindness, kidney failure, and amputations
- Major risk factor for heart disease, stroke, and birth defects
- Leads to higher death rates from pneumonia, influenza, and other illnesses
- Shortens average lifespan by up to 15 years
- Costs more than \$105 billion annually, including direct and indirect costs (i.e. disability, work loss, and premature death)



diabetes when she becomes pregnant, thus setting in motion a vicious cycle that rapidly spreads diabetes from one generation to the next.

NIDDK funds an extensive portfolio of basic, clinical, epidemiologic, and behavioral research aimed at revealing the genetic and environmental factors that contribute to the disproportionate burden of diabetes in minority populations.

Advances in understanding the underlying causes of diabetes are helping to determine the factors that account for the higher rates of diabetes in minority groups. The Institute's *Strategic Plan on Minority Health Disparities* outlines research programs that comprehensively address diabetes and obesity as well as other diseases affecting minorities in greater numbers.

## Blood Glucose Control

Though now an accepted tenet of diabetes treatment, the importance of intensive blood glucose control was not widely recognized before 1993, when researchers announced the results of a landmark clinical trial funded by the NIDDK. The Diabetes Control and Complications Trial (DCCT) changed conventional thinking about the management of type 1 diabetes by clearly showing that tight control prevented or delayed the eye, kidney, and other complications of diabetes. And the benefits of tight control endured for years, according to a recent follow-up study of DCCT participants. Another major study, the United Kingdom Prospective Diabetes Study, confirmed the value of intensive control for people with type 2 diabetes as well.

As any parent of a diabetic child knows, achieving tight control with insulin injections can be difficult and frustrating. Recent improvements in glucose-sensing devices that eliminate the need for finger sticks are helping people control their blood sugar more easily. The NIDDK is continuing to support research in noninvasive glucose monitoring and other approaches that may result in improved treatments for diabetes and its complications, while pursuing the ultimate goal of finding a true cure for this debilitating disease.

The DCCT findings made it clear that patients and health care providers alike needed to hear about the importance of intensive control. Through the National Diabetes Education Program (NDEP), the NIDDK and the Centers for Disease Control and Prevention are working hard to increase awareness of diabetes and to encourage patients and their health care team to manage

promote early diagnosis, and ultimately, to prevent the onset of diabetes. For more information, see "Information, Education, and Outreach."

## Islet Transplantation

Recently, a research team led by Dr. James Shapiro at the University of Alberta in Edmonton, Canada, announced promising results with islet transplantation in seven patients with type 1 diabetes. At the time of the report in *The New England Journal of Medicine*, all seven patients who had received the transplants remained free of insulin injections up to 14 months after the procedure.

The Immune Tolerance Network supported by the NIH and the Juvenile Diabetes Foundation is conducting a clinical trial that seeks to replicate the University of Alberta results at ten



**Dr. Anne Sumner tests volunteer's metabolic rate.**

diabetes more aggressively. In addressing the gap between current and desired diabetes care and practices, the NDEP strives to improve treatment and outcomes for people with diabetes, to

medical centers in the United States and Europe. If the results of this trial are promising, additional trials will be planned for a larger number of patients. With the insights gained from this



**Researchers identify portal vein before islet transplantation.**

research, scientists hope to further refine islet harvesting and transplantation and learn more about the immune processes that affect rejection and acceptance of transplanted islets.

To track islet transplant outcomes, the NIDDK will support the creation of a North American islet transplantation registry, which will collect and analyze data on patient and graft survival rates and other information to help researchers evaluate progress in the promising field of islet transplantation.

Research conducted and supported by the NIH, including basic discoveries in immunology and cell and transplant biology, laid the groundwork for the Edmonton advance. In 1972 NIDDK grantee Dr. Paul Lacey of Washington University first reported that islet transplantation could cure diabetes in rats. At the University of Minnesota, Dr. David Sutherland proved that a patient whose pancreas had to be surgically removed could achieve insulin independence by having his or her own islets harvested and transplanted back. Until the

Edmonton advance, however, attempts at islet transplantation fared poorly: less than 5 percent of people who received transplanted islets along with immunosuppressive drugs were able to stay off insulin longer than one year.

Despite these disappointing results, several avenues of research were producing many improvements in organ transplantation and in the drugs that prevent rejection—all of which paved the way for the Edmonton advance. Dr. Thomas Starzl of the University of Pittsburgh, a longtime NIDDK grantee and premier liver transplant researcher, pioneered the use of FK-506. Now known as tacrolimus, FK-506 is an anti-rejection drug used by the Edmonton team.

Scientists also improved islet isolation techniques and ways to assess islet function. Another NIDDK grantee, Dr. Camilo Ricordi of the University of Miami, refined the method for isolating islets from pancreatic tissue and preserving them in what is now called the “Ricordi Chamber.”

Despite the promise of islet transplantation, certain obstacles, such as the inadequate supply of donor islets and the need for immunomodulatory drugs, must be overcome before this technique is adopted as a standard treatment for type 1 diabetes. For information about NIDDK research initiatives that address these barriers, see “Autoimmunity and the Beta Cell.”

## **Diabetes Research Working Group**

In 1999 the Congressionally-established Diabetes Research Working Group (DRWG), a panel of diabetes experts, issued its Strategic Plan and recommendations for future diabetes research. (The DRWG report is on the NIDDK Web site under “Special Reports, Planning, Coordination, and Testimony.”) The NIH is pursuing the full range of the DRWG’s scientific recommendations, with special emphasis on five areas of extraordinary opportunity: genetics, obesity, autoimmunity and the beta cell, cell signaling and cell regulation, and clinical research and clinical trials. Following are examples of research advances and initiatives in these areas.

## **Genetics of Diabetes and Its Complications**

Diabetes encompasses a group of diseases that impair blood glucose regulation. Some rare forms of diabetes are caused by the mutation of a single gene. The common forms (type 1 and type 2),



however, are complex diseases that arise from genes interacting with other genes and the environment. When these susceptibility genes combine with environmental triggers—possibly viruses in type 1 diabetes or diet, obesity, and inactivity in type 2—the risk of getting diabetes rises. Still other genes may heighten the risk of developing severe complications after the onset of diabetes.

For years, scientists have known that single-gene mutations contribute to rare forms of diabetes, such as Maturity Onset Diabetes of the Young (MODY) and other rare subtypes of type 2 diabetes, which may account for up to 5 percent of diabetes cases. Five MODY genes, all involved in some aspect of regulating insulin secretion, have been identified. For example, a mutation in one copy of the gene insulin promoter factor-1 causes a rare

interacting to create susceptibility. By developing new techniques and studying larger patient populations, researchers are working hard to find these genes and understand their functions. An International Type 2 Genetic Linkage Consortium has been formed to help investigators combine their individual studies and localize diabetes genes.

Recently, a team of NIDDK-supported researchers led by Drs. Graeme Bell and Nancy Cox of the University of Chicago identified a gene called NIDDM1 on chromosome 2, which interacts with a gene on chromosome 15 to increase the risk of developing type 2 diabetes. A subtle variation in the sequence of the NIDDM1 gene, which encodes a protease called calpain 10, raises the risk of type 2 diabetes in a Mexican American and two northern European populations. Further clinical studies and investigations of calpain 10 in cultured cells and transgenic animals will shed light on the gene's role in diabetes. By finding the gene, scientists have moved a step closer to understanding how type 2 diabetes arises and have identified a new target for drug development.

Research has shown that the strongest genes predisposing to type 1 diabetes are alleles, or common genetic variations, of the major histocompatibility complex (MHC), mainly HLA DR3 and DR4. These molecules play a major part in activating T cells and regulating the immune response. In addition to the HLA genes, there are environmental influences as well as other genes that influence susceptibility to type 1 diabetes. NIDDK plans to support a consortium to foster collaboration of research teams searching for these genes.

The NIDDK funds many studies on the complications of diabetes, including the search for genes that predispose people to complications such as kidney disease. Certain populations, such as the Pima Indians of Arizona, have a high incidence of kidney disease from diabetes (KDDM), and studies have shown that susceptibility to this complication runs in families. An NIDDK study of 715 Pima families recently found that one gene with a major effect can explain susceptibility to KDDM, though other genes probably play a role.

Researchers in NIDDK's Familial Investigation of Nephropathy of Diabetes program are now studying siblings of people with diabetes, some who have kidney disease and some who do not, in hopes of finding genes unique to those who have kidney disease. Once the gene or genes have been found, scientists will try to develop targeted drugs and other prevention strategies.

## Autoimmunity and the Beta Cell

In the past decade, major discoveries in immunology and cell biology have helped to clarify the immunologic basis of type 1 diabetes. To capitalize on these gains, the NIH supports many initiatives that are searching for ways to block immune destruction of the beta cell and spur strategies to replace beta cell function. One initiative calls for researchers to develop methods for imaging beta cells so scientists can evaluate their mass, function, and signs of inflammation. Such imaging techniques will help doctors monitor disease progression and response to therapy in people who have diabetes or are at risk for developing it.



**Islets are isolated from donor pancreas.**

form of early-onset type 2 diabetes, while a mutation in both copies leads to failure of the entire pancreas to develop.

Unlike single-gene disorders, the more common forms of diabetes appear to arise from subtle defects in several genes, each contributing and probably

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## *Major discoveries in immunology and cell biology have helped to clarify the immunologic basis of type 1 diabetes.*

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The University of Alberta's advance in islet transplantation has infused hope and excitement into the diabetes community. However, even if clinical trials confirm the procedure's value in treating type 1 diabetes, two obstacles may hamper its use as a standard treatment. One is the potentially harmful long-term effects of immunosuppressive drugs needed to prevent rejection of the transplanted islets. This concern especially applies to children, who would face a lifetime of immune suppression. Another issue is the limited supply of donor pancreases, from which islets are extracted. Only a few thousand become available each year, far short of the number needed.

Intensive research is yielding advances on both fronts. To circumvent the need for immunosuppressive drugs, scientists are working on immune modulators that prevent T-cell rejection of donor tissue without endangering the patient's disease-fighting ability. This work, which builds on a growing body of knowledge about the molecular signals governing immune cell communication, has exciting implications for preventing transplant rejection and treating diseases of the immune system, such as autoimmunity and immunodeficiency.

Addressing the shortage of donor pancreases, NIH-supported researchers at various medical centers are using genetic engineering methods to induce the development of functional beta cell lines. A team at the University of California at San Diego recently reported success in developing the first human beta cell line that produces insulin in response to glucose. Further studies will reveal whether these cells can retain their insulin-producing ability over the long term and safely be transplanted into people with diabetes.

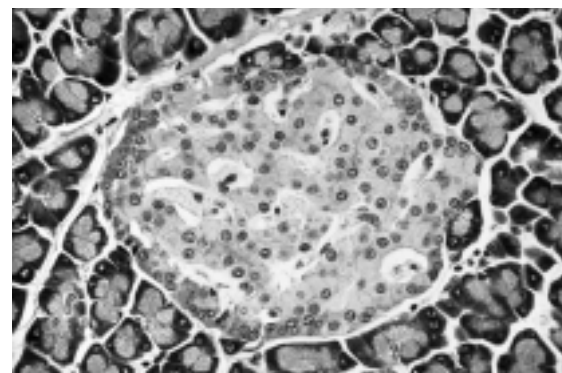
NIDDK is also encouraging researchers to develop a cell culture model of the human beta cell that responds to glucose, reflects signaling through cell surface and nuclear receptors that regulate insulin production and secretion, and responds to growth factors and cytokines active in the pancreatic beta cell.

Stem cell research holds much promise for treating many diseases such as diabetes, cancer, Parkinson's disease, and Alzheimer's disease. Pluripotent stem cells, derived from the inner cell mass of human embryos at the blastocyst stage and from fetal tissue, are capable of limitless division and self-renewal. These stem cells might be stimulated to develop into specialized cells such as beta cells. Adult stem cells that reside in the pancreatic duct and other organs may also have the capacity to differentiate into specialized cells such as beta cells, but much more research is needed to determine their potential.

## **Cell Signaling and Cell Regulation**

Research in cell signaling and regulation holds the key to understanding the biochemical pathways that maintain normal metabolism and go awry in obesity, insulin resistance, and type 2 diabetes. The NIDDK supports a great deal of research in these processes, which underlie critical functions such as insulin action, immunity, appetite regulation, and beta cell activity. Many of the same molecules are key regulators in a variety of tissues. For example, only recently have scientists realized that fat cells are an active endocrine organ, secreting leptin, tumor necrosis factor-alpha, interleukin-6, complement C3, and other cell-signaling substances. It is critical to learn how these hormones and cytokines affect other tissues and influence the risk of diabetes.

Research in cell signaling, communication, and regulation is helping scientists understand the normal workings of the immune system and what goes wrong in autoimmune disorders such as type 1 diabetes, inflammatory bowel disease, and common thyroid disorders. Cell signaling work is also shedding light on insulin resistance, a disorder that usually accompanies, and often



**A healthy pancreatic islet**



**Dr. Phillip Gorden conducts insulin studies.**

precedes, type 2 diabetes. This condition occurs when muscle, fat, and liver cells lose the ability to respond normally to insulin, the hormone released by the glucose-sensing beta cells of the pancreas. Scientists once thought that insulin resistance arose from a defect in the insulin receptor, but they are now moving toward a deeper understanding of the intricate intracellular pathways that disrupt the balance between insulin action and insulin secretion.

Researchers at Harvard University's Joslin Diabetes Center are focusing on two proteins, IRS-1 and IRS-2, which become activated inside the cell when insulin binds to the receptor. IRS-1 and -2 then interact with other proteins in a complex signaling pathway that arouses the glucose transporter, which ferries glucose into the cell. The IRS complex also triggers a second pathway, the Ras complex, which turns on gene expression inside the cell.

In more recent studies in knock-out mice, the Joslin team found that insulin, acting through receptors in the brain, plays a key role in regulating appetite, fat accumulation, and even reproductive function. When insulin is taken up by receptors in the brain, it appears to have an appetite-suppressing effect. Without these receptors, mice became obese, insulin resistant, and abnormal in their reproductive function. These findings are reinforcing scientists' belief that a complex network of molecular signals and feedback loops involving the brain and other tissues is the key to understanding satiety, obesity, insulin resistance, and the development of type 2 diabetes. Continuing research with animal models is clarifying the specific roles of these molecules in muscle and liver cells, where insulin resistance appears to occur.

The NIDDK is also stimulating research on the role of nuclear hormone receptors in regulating gene expression in specific tissues and on growth factors that regulate beta cell growth. Several growth factors are already being tested in clinical trials for the treatment and prevention of microvascular disease, a complication of diabetes.

## Clinical Research

Laboratory and animal studies can answer basic biologic questions and yield potential therapies, but only clinical research, or human studies, can determine whether proposed treatments and prevention strategies are safe and effective in people.

If diabetes could be prevented or delayed, many thousands of people would enjoy improved health and freedom from the cost and burden of managing the disease. Complete prevention will only be possible when scientists have a clear understanding of the causes of diabetes. However, enough is currently known about factors that contribute to diabetes risk that two large multicenter clinical trials funded by the NIDDK are trying to prevent diabetes in high-risk groups.

The **Diabetes Prevention Program (DPP)** seeks to determine whether type 2 diabetes can be prevented or delayed in people who have impaired glucose tolerance, a condition in which blood glucose levels are higher than normal but not yet diabetic. The study compares two different approaches to prevention—an intensive regimen of diet and exercise versus treatment with metformin, a diabetes medication—to a

control group provided standard advice on diet and exercise. About 45 percent of the 3,000 DPP participants are minority group members.

In one of the most important discoveries of the past 20 years, scientists learned that type 1 diabetes results from



the slow autoimmune destruction of the pancreatic beta cells, a process that begins long before the appearance of diabetes symptoms. Most patients who develop type 1 have markers for the disease in their blood—antibodies against certain beta cell proteins, including insulin, glutamic acid decarboxylase (GAD), and the enzyme IA2. By measuring these markers of autoimmune activity and genetic markers, scientists can now gauge a person's risk for developing type 1 diabetes.

This new understanding of the immune basis for type 1 diabetes and

other insights gained from immunology research opened the possibility of modulating the immune system to prevent beta cell destruction. Capitalizing on these converging discoveries, an NIDDK-supported multicenter trial called the **Diabetes Prevention Trial-Type 1** is testing whether insulin injections or oral insulin can prevent type 1 diabetes in high-risk individuals—people who have close relatives with type 1 diabetes, high levels of islet cell antibodies, and other indicators of risk. For more information about this trial, call 1-800-HALT-DM1.

Through creation of the **Type 1 Diabetes Mellitus TrialNet**, the NIDDK will expand the clinical trial infrastructure to speed studies of new agents that preserve beta cell function and prevent type 1 diabetes.

The cells lining the heart and blood vessels function abnormally in diabetes. To learn more about the factors contributing to atherosclerosis and microvascular complications, the NIDDK has an initiative to study how diabetes affects endothelial cells and how these changes lead to blood vessel damage. NIDDK also supports two multicenter clinical trials of the National Heart, Lung, and Blood Institute (NHLBI) that will try to define the factors that contribute to heart disease in diabetes and the most effective ways to treat it:

- **Action to Control Cardiovascular Risk in Diabetes (ACCORD)** compares the effects of standard versus intensive treatment of blood glucose, high blood pressure, and lipids on the development of cardiovascular disease in people with diabetes; and

- **Bypass Angioplasty Revascularization Investigations (BARI II)** examines the effects of insulin-providing and insulin-sensitizing strategies in people with type 2 diabetes who have significant coronary artery disease.

NIDDK, with NHLBI support, is launching a third national multicenter trial, the **Study of the Health Outcomes of Weight Loss (SHOW)**, to assess how intentional weight loss affects cardiovascular disease and other health parameters such as blood sugar, muscle mass, bone strength, and microvascular disease in obese people with type 2 diabetes. The study will try to answer two major questions:

- Do interventions designed to produce sustained weight loss in obese people with type 2 diabetes improve health?
- How do the benefits and risks of these interventions compare with the benefits and risks of treating obesity-related conditions without weight loss?

### More Information About Diabetes

Visit NIDDK at  
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